REMARKS

Applicant respectfully requests reconsideration of this application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Upon entry of the amendments, claims 1, 3-15 and 17-39 will be pending. Claims 1 and 3 presently are being amended. Exemplary support for the amendments to claim 1 exists in original claims 2 and 3. Claims 2, 16 and 40-93 presently are being canceled, without prejudice or disclaimer. No claims presently are being added.

Because the foregoing amendments do not introduce new matter, entry thereof is respectfully requested.

II. The Claims Are Patentable Over U.S. Patent No. 4,540,602

Claims 1-12, 17 and 24-39 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 4,540,602 ("the '602 patent"). According to the rejection, the '602 patent discloses pharmaceutical compositions that comprise nifedipine in association with gum Arabic and gelatin surface modifiers. The nifedipine particles of the '602 patent allegedly have a diameter of 0.1 – 3.0 microns. Applicant respectfully traverses the rejection.

The '602 patent is directed to a process comprising dispersing in water a poorly water-soluble solid drug in the presence of a water-soluble high-molecular substance to form a disperse system. The system contains the drug in the form of finely divided particles substantially not greater than 10 microns in diameter. The dispersion medium is then removed from the disperse system to form a pharmaceutical composition consisting of the finely divided drug coated with the water-soluble high-molecular substance. *See*, '602 patent, col. 2, lines 21-30.

This reference does not teach or suggest Applicants' claimed composition having an effective average particle size of less than about 1000 nm. Moreover, the reference does not teach a composition having a ***crystalline*** drug.

A. The Method of the '602 Patent Results in Amorphous, and Not Crystalline, Drug Particles

The '602 patent refers to four methods for forming the described composition: (i) the drug is dissolved in an aqueous alkaline solution, and the resulting solution is then neutralized with an acid to precipitate the drug; (ii) the drug is dissolved in an aqueous acid solution, and the resulting solution is then neutralized to precipitate the drug; (iii) the drug is dissolved in a hydrophobic organic solvent, and the resulting solution is emulsified in water; and (iv) the drug is pulverized in water. *See*, '602 patent, col. 2, lines 45-64.

The first two methods refer to dissolving the drug in a solvent, followed by precipitation of the drug. *See e.g.*, col. 6, lines 23-30 (method 1); and col. 6, lines 43-48 (method 2). The third method refers to dissolving the drug followed by emulsification. For all three of these methods, the drug will be in an amorphous state and not in a crystalline state. In contrast, Applicant's claimed invention is limited to crystalline drugs. Moreover, the '602 patent emphasizes that the third method is preferred, as the drug is allegedly more soluble when in an amorphous state. *See*, '602 patent, col. 5, line 39; and col. 8, lines 53-55.

A noncrystalline or amorphous form has no molecular structure. *See, Hawley's Condensed Chemical Dictionary,* 11th Edition, page 73 (Van Nostrand Reinhold Co., New York, NY 1987) (Exhibit 1). In contrast, crystalline structures have characteristic shapes and cleavage structures due to the arrangement of their molecules, which comprise a definite pattern called a lattice. *See, Hawley's Condensed Chemical Dictionary* at 325 (Exhibit 1).

The third method, which results in amorphous drug particles, is the only method taught by the '602 patent that produces compositions having small particle sizes. *See, e.g.*, Example 6 (particles within the range of 100 to 1500 nanometers), Example 8 (100 to 3000 nm), Example 9 (400 to 1800 nm), Example 10 (100 to 1200 nm), Example 12 (100 to 500 nm), and Example 13 (100 to 500 nm).

B. The '602 Patent Does not Teach Compositions Comprising Crystalline Drug Particles Having an Effective Average Particle Size of Less than 1000 nm

Applicant teaches and claims a nanoparticulate composition having "an effective average particle size of less than about 1000 nm." This is defined in the application as a composition in which "at least 50% of the particles have an average particle size of less than about 1000 nm." *See,* paragraph [0130] of the application.

The '602 patent teaches that "as the particle size of a drug decreases, its surface area increases and, therefore, its absorption into a body becomes quicker." *See*, '602 patent, col. 4, lines 44-46. Thus, a composition having an effective average particle size of 1000 nm is greatly preferred over a composition "ranging up to 10 microns," such as that disclosed by the '602 patent.

C. The "Pulverizing" Method of the '602 Patent Does Not Teach Applicant's Claimed Compositions

The fourth method of the '602 patent for making the described compositions refers to pulverizing in an aqueous solution a water-soluble high-molecular weight substance, followed by removing the water from the resulting aqueous dispersion. *See*, '602 patent, col. 9, lines 43-49. The '602 patent teaches that this method results in particles having a size ranging from 500 nm or less to 5000 nm in diameter. *See*, '602 patent, col. 10, lines 15-17. This does not teach Applicant's' claimed compositions, in which at least 50% of the particles have a particle size of less than about 1000 nm.

Examples 14-18 use the fourth method of the '602 patent in preparing the described compositions. Example 14 teaches a composition having particles "within the range of 0.5 to 5 microns" (col. 16, lines 13-15); Examples 15, 16, and 18 do not refer to resultant particle size. Example 17 refers to a composition prepared by wet grinding, heating the resultant dispersion to effect gelation, and recovering and drying the precipitate. The "diameters of most redispersed particles were not greater than 0.5 microns." *See*, '602 patent, col. 17, lines 50-68. This does not teach the claimed invention, directed to compositions in which at least 50% of the particles have a size of less than 1000 nm.

To confirm that the fourth method of the '602 patent does not teach or suggest Applicant's claimed invention, Applicant duplicated Examples 15 and 18 of the '602 patent, the results of which are attached as Exhibit 2. The results show that, using the technique according to Examples 15 and 18 of the '602 patent, a submicron size was not obtained for the resultant acetophenetidin composition.

For at least these reasons, the '602 patent does not teach or suggest the claimed invention.

III. The Claims Are Patentable Over GB Patent Application No. 2166651

Claims 1-15, 17 and 24-39 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by GB patent application No. 2166651 ("the '651 application"). According to the rejection, the '651 application discloses pharmaceutical compositions that comprise nifedipine in association with hydroxyalkyl celluloses and polyvinylpyrrolidone surface modifiers. The nifedipine particles of the '651 application allegedly have an average size of between 0.1 and 125 microns. Applicant respectfully traverses the rejection.

The '651 application neither teaches nor suggests nifedipine particles having an effective average particle size of less than about 1000 nm, as recited in the claims. Particles in the '651 application allegedly range in size from 0.1 to 125 microns, but in the presently claimed invention at least about 50% of the nifedine particles have a size less than about 1000 nm. *See,* US 2004/0115134, ¶ 0162 (describing "effective average particle size"). This is significant, as a composition having a widely variable particle size, like that in the '651 patent, will not exhibit uniform dose response. The dissolution and resultant absorption of nifedipine corresponds to the drug particle size. *See,* US 2004/0115134, ¶ 0024.

Additionally, nifedine particles of the '651 application actually ranged in size from 10 to 180 microns and had an average particle size greater than 90 microns. Example 3 of the '651 application describes the preparation of "micro-particles" containing nifedipine. According to that example, microscopic examination revealed particle sizes ranging from 10 to 180 microns, with the "major proportion of particles" being greater than 90 microns in diameter. *See,* the description of methods in Example 1. There was no suggestion that smaller nifedipine particles, as recited by the pending claims, should be made.

Thus, the '651 application neither anticipates nor renders obvious the pending claims, and Applicant therefore requests withdrawal of the anticipation rejection.

IV. The Claims Are Patentable Over U.S. Patent No. 4,562,069

Claims 1-15, 17 and 24-39 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 4,562,069 ("the '069 patent"). According to the rejection, the '069 patent describes combining nifedipine crystals having a mean particle diameter of about 1 to 10 microns with a PVP or methylcellulose surface stabilizer. Applicant respectfully traverses the rejection.

The '069 patent lacks any teaching of nifedipine particles having an effective average particle size of *less than* about 1000 nm, as recited in the claims. The '069 patent also lacks any suggestion to reduce the nifedipine particle size into that range.

Thus, the '069 application neither anticipates nor renders obvious the pending claims, and Applicant therefore requests withdrawal of the anticipation rejection.

V. The Claims Are Patentable Over U.S. Patent Nos. 4,814,175 & 5,145,684

Claims 1-15, 17-18 and 24-28 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 4,814,175 ("the '175 patent") and U.S. Patent No. 5,145,684 ("the '684 patent"). According to the rejection, the '175 patent teaches combined preparations of nifedipine and a beta blocker. The compositions allegedly contain PVPP, cellulose and sodium alginate surface modifiers. As acknowledged by the Examiner, the '175 patent is deficient because it teaches nifedipine particle diameters of 10-50 microns. According to the rejection, however, the '684 patent teaches that particle sizes of less than 400 nm confer high bioavailability to poorly soluble drugs, which would have motivated the skilled artisan to produce the presently claimed invention. Applicant respectfully traverses the rejection.

The '175 and '684 patents are directed to solving contrasting problems. The '175 patent relates to delayed release nifedipine compositions ('175 patent, abstract) that have the advantage of achieving 24-hour effectiveness ('175 patent, column 2, lines 3-7). To obtain the delayed release profile, larger diameter particles of nifedipine are employed, specifically

particles that are 10-50 microns and preferably 15-50 microns in diameter. By contrast, the '684 patent relates to maximizing drug bioavailability by minimizing drug particle size, preferably to a size less than 400 nm. *See*, '684 patent, column 2, lines 31-43. The '684 patent does not mention nifedipine in this context.

Given the '175 patent, the artisan of ordinary skill would understand that the major challenge with nifedipine preparations was to obtain *timed or delayed release*. The patent makes no mention that bioavailability, the subject of the '684 patent, is a problem with nifedipine. In fact, it states that others already had addressed bioavailability issues for nifedipine. *See*, '175 patent, column 1, lines 9-20. The artisan of ordinary skill reading the '175 patent, therefore, would be motivated only to create an extended release nifedipine composition and to employ larger diameter drug particles in doing so. That is entirely contrary to the purpose and teachings of the '684 patent, which does not even mention nifedipine.

Thus, the artisan of ordinary skill had no motivation to combine the teachings of the '175 and '684 patents. For at least this reason, Applicant requests withdrawal of the obviousness rejection.

VI. Concluding Remarks

This application is now in condition for allowance, and requests favorable reconsideration of it. If the Examiner believes that any issues remain unresolved or that an interview would help to advance prosecution, he is invited to contact the undersigned attorney by telephone.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for

such extensions under 37 C.F.R. §1.136 and authorizes payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 7/27/06

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